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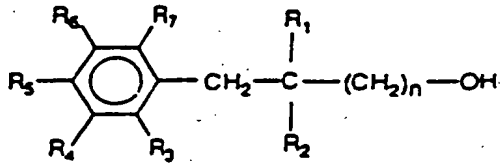
(54) Title: BIOCIDAL ALCOHOLS, THEIR PRODUCTION AND THEIR USE

(57) Abstract

Biocidal alcohols of general formulae (I) and (II) are described in which R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl, R_1 is a significance of R_2, independently of R_2, or in compounds of formula (I) is hydrogen, each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and n is 1 or 2.



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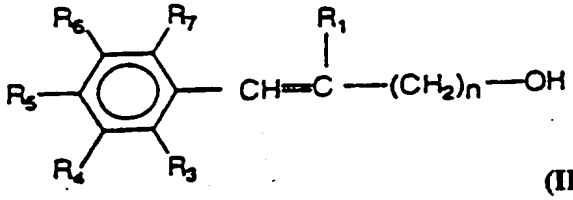

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Biocidal alcohols, their production and their use

The invention relates to biocidal alcohols, their production and their use. In particular, the invention relates to a group of antimicrobially, fungicidally and antimycobacterially effective alcohols, to a process for their production and to the use of these alcohols in disinfectants, antiseptics, antimycotics, deodorants and preservatives.

The antimicrobial action of aliphatic alcohols is sufficiently known. Their disinfecting action increases with increasing chain length and reaches an optimum, say, in the case of 1-octanol. Primary alcohols are generally more effective than the corresponding secondary alcohols, and these in turn surpass the action of the corresponding tertiary alcohols, i.e. the action decreases e.g. in the order n-butanol - sec. butanol - tert. butanol.

2-ethyl hexanol has proved particularly effective. Unfortunately, however, this alcohol has an intensive and unpleasant odour which cannot be masked in practice by adding various perfumes. Its use as an active ingredient in disinfectants or preservatives is therefore severely limited.

The alcohols usually used, ethanol, isopropanol and n-propanol usually have to be used in concentrations of more than 50 % by wt. for the disinfection of surfaces. To deactivate viruses which are important as regards hygiene - such as e.g. Hepatitis B - the alcohol contents of hand disinfectants have to be increased to above 80 % by wt.

Disinfectants with high alcohol contents have a series of disadvantages such as for example low flash points, inadequate material compatibility above all with plastics such as e.g. plexiglas, a rapid evaporation from the skin and surface areas

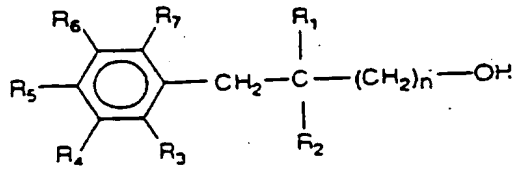
to be disinfected and thus no sufficient long term action, such as is e.g. indispensable for surgical hand disinfection, and an incompatibility with mucous membranes and wounds; concentrations of above 10 % by wt. already lead to an unpleasant burning.

From the series of alkyl aryl alcohols, benzyl alcohol, phenethyl alcohol and 3-phenyl-1-propanol are known to be antimicrobially effective. Benzyl alcohol is relatively easily oxidized to benzaldehyde which draws attention to itself in practice by its smell of bitter almonds. Phenethyl alcohol is the main constituent of rose oil and determines the character of the odour particularly when used for preserving cosmetics. Because of their weak action against fungi, both benzyl alcohol and phenethyl alcohol have to be combined with other active ingredients. 3-phenyl-1-propanol definitely presents itself as an antimicrobial active ingredient because of its pleasant and mild odour; however, its antimicrobial action, is unfortunately not sufficient for it to be used by itself as a disinfectant or preservative.

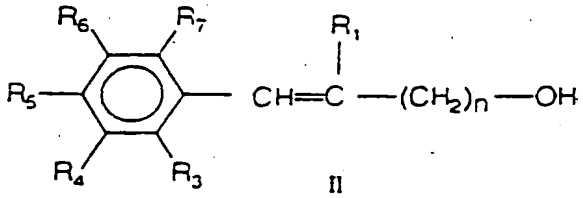
Also known is the antimicrobial action of the phenoxyalkanols, e.g. phenoxyethanol or 2-phenoxy-1-propanol. It is also used in practice for preserving cosmetics. The effectiveness - particularly against fungi - does however demand a relatively high use concentration. These alcohols have therefore to be combined with other active ingredients, e.g. with cationic compounds and/or aldehydes, particularly for the production of disinfectants.

It is therefore the object of the invention to find especially antimicrobially and fungicidally effective alcohols which, used alone or in combination with the aforementioned alcohols, produce disinfectants or preservatives which are characterized by a reduced total alcohol content, an excellent action against microorganisms - preferably against fungi - and an acceptable odour.

To achieve this object, the novel compounds (alcohols) of general formulae I and II are proposed according to claim 1:



I



II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

with the proviso, that in compounds of formula I

i) where R_1 and all groups R_3 to R_7 are hydrogen, then n = 2;

ii) where R_1 and R_2 are C_1-C_6 alkyl and all groups R_3 to R_7 are hydrogen, then n = 2;

iii) where R_1, R_2 and R_4 are methyl and all groups R_3 and R_5 to R_7 are hydrogen, then n = 2;

iv) where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is methyl or methoxy, then n = 2;

v) where R_1, R_3, R_6 and R_7 are hydrogen, R_2 is methyl and R_4 and/or R_5 are H or C_1-C_6 alkyl, then n = 2;

vi) where R_1 and R_4 to R_7 are hydrogen, R_2 is methyl and R_3 is methyl or methoxy, then n = 2;

vii) where R_1, R_3, R_5 and R_7 are hydrogen, R_2 is methyl, R_4 and R_6 are methyl or R_4 is hydrogen and R_6 is methyl, then n = 2;

and with the proviso, that in compounds of formula II

where R_1 is methyl or pentyl and all other groups R_3 to R_7 are hydrogen, then n = 2.

These alcohols can be produced in accordance with the process according to Claim 10 or 11.

Preferred embodiments are the subject-matter of the dependent claims.

It has surprisingly been shown that the action of the parent compound of the alcohols according to the invention, i.e. 3-phenyl-1-propanol or 4-phenyl-1-butanol or the corresponding propenols or butenols, in particular against fungi, is significantly increased when substituents are introduced into the 2-position in the case of the propanols, i.e. n = 1, or into the 3-position in the case of the butanols, i.e. n = 2, and optionally additionally into the aromatic core.

In preferred embodiments

R_2 is selected from C_1-C_5 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_5 alkenyl and C_3-C_5 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is hydrogen, fluorine, chlorine or bromine,

and preferably

R_2 is methyl ethyl, ethenyl, propyl, propenyl, propargyl, butyl and amyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, is hydrogen, methyl-X-, ethyl-X-, ethenyl-X-, propyl-X-, propenyl-X-, propargyl-X, isopropyl-X, isopropenyl-X-, t-butyl-X-, methoxymethyl-X-, methoxyethyl-X-, ethoxymethyl-X-, ethoxyethyl-X-, methoxypropyl-X- or ethoxypropyl-X-, where X is -O- or -S-.

It is preferred that n = 1.

Any combinations of groups according to the above definitions are also possible.

These alcohols according to the invention are suitable as antimicrobial and fungicidal active ingredients for disinfectants, antiseptics, antimycotics, deodorants and preservatives.

The invention covers also a composition which contains at least one of said compounds of formula I or II and a compound selected from alcohols, surfactants and solvents. It is preferred that the composition contains a compound of formula I or II in a quantity of 0.01 to 10 % by wt., in particular 0.05 to 8 % by wt. and preferably 0.1 to 5 % by wt. More preferred a composition according to the invention contains

a) 0.01 to 10 % by wt. of a compound of formula I or II, and

b) 0.1 to 90 % by wt. of a compound selected from C_1-C_6 alkyl alcohols, unsubstituded or substituted with a C_6-C_{12} aryl, aralkyl or aryloxy group, anionic, cationic, amphoteric or nonionic surfactants, dimethylformamide, betaines and glycerine.

Preferred compounds summarized in b) are, for example, ethyleneglycol ethers such as "Rewopal MPG 40" (which is tetraethyleneglycol monophenyl ether), ethoxylated higher alkyl alcohols such as "Brij 58" (which is polyoxyethylene-20-cetylalcohol), ethanol, 1-propanol, 2-propanol sulfosuccinate, betaine, phenoxyethanol and phenethylalcohol.

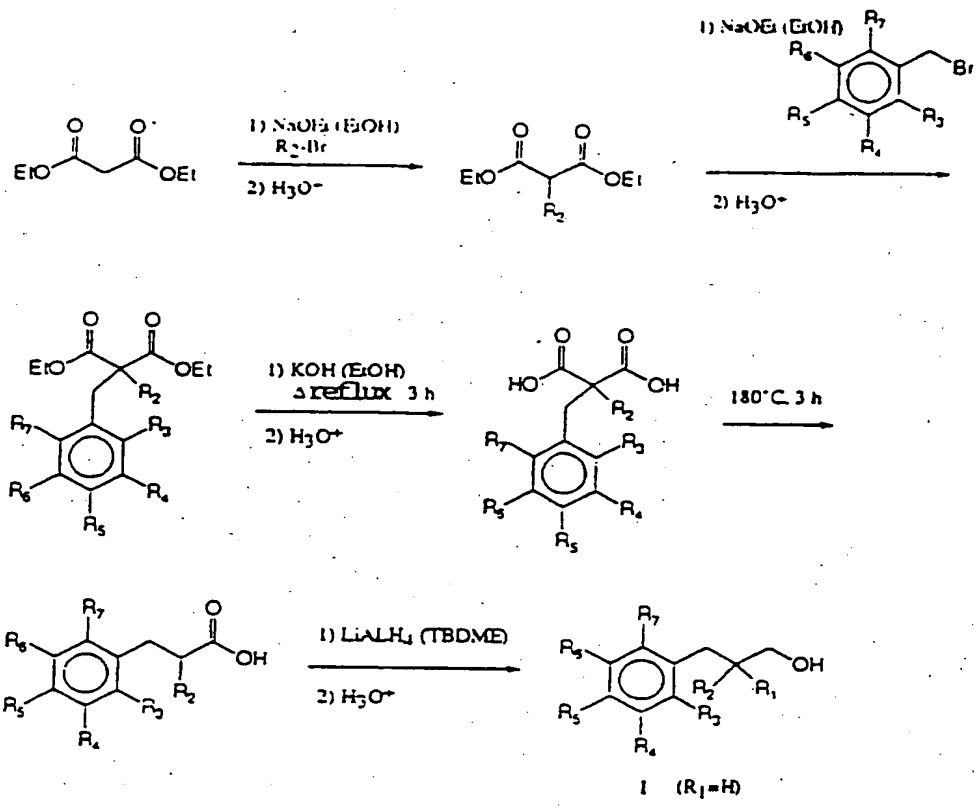
Said alkyl alcohols or mixtures thereof may be present in an amount of 20 to 85 % by wt., specifically 25 to 80 % by wt. Said surfactants or mixtures thereof may be present in an amount of 1 to 30 % by wt., specifically 5 to 25 % by wt. The other mentioned compounds may each be present in an amount of 0.1 to 20 % by wt., specifically 0.5 to 20 % by wt, e.g. 1.0, 2.0 or 3.0 and up to 10 or 12 % by wt.

The invention also covers the production of said compounds of formula I or II. Described in DE 35 31 585 is the production of such alcohols using Grignard reactions. However, the disadvantages of Grignard reactions are adequately known.

The process according to the invention offers several advantages over the Grignard processes. It is particularly advantageous that according to the invention all alcohols of general

formula I can be produced according to the same process. This is a malonic ester synthesis with subsequent decarboxylation and reduction. In the case of n = 2, the alcohols of general formula I can be obtained via the compounds of formula II using alkylation instead of hydrogenation.

This uniform and simple process consists of the following reaction steps:



I (R_1=H)

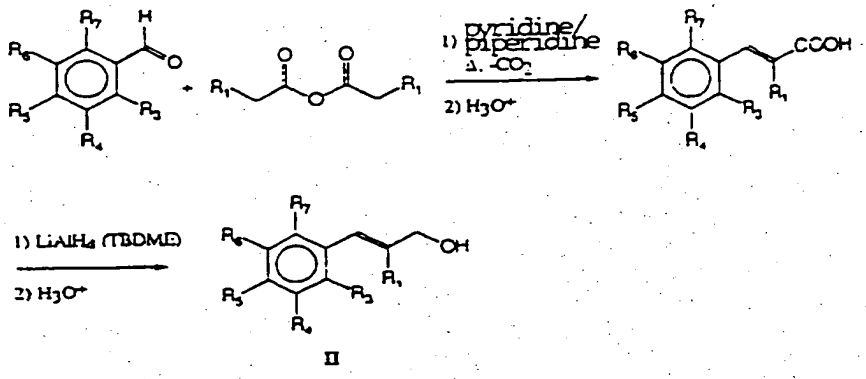
1. Alkylation of dialkyl malonate, preferably diethyl malonate with an alkyl halide, preferably a bromide, to give the monosubstituted malonic ester, as a result of which the group R_2 is introduced.

2. Second alkylation with an aryl-substituted benzyl halide, preferably a chloride or bromide, as a result of which the groups R_3 to R_7 are introduced, provided they are not hydrogen.

3. Saponification and subsequent decarboxylation to give the 3-aryl-substituted propionic acid and treatment by distillation of same.

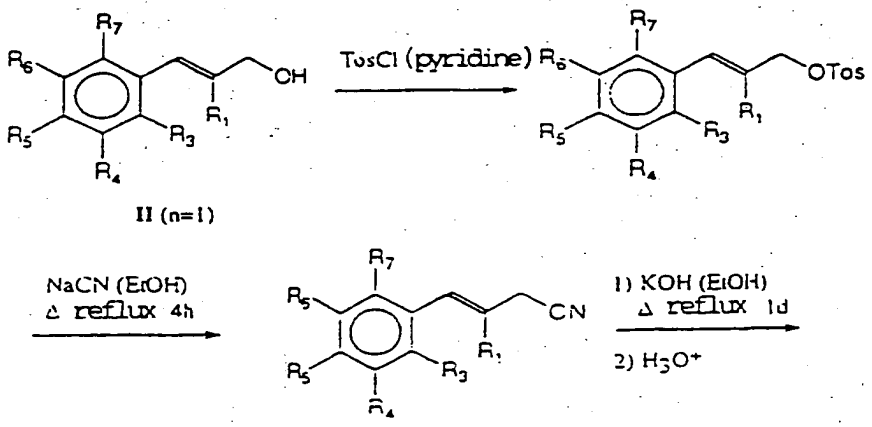
4. Reduction to the desired alcohol of formula I, e.g. with lithium aluminium hydride in diethyl ether or tert.-butyl methylether.

The alcohols of formula II with n = 1 can for example be obtained via a Perkin condensation reaction of a corresponding aromatic aldehyde with anhydrides with simultaneous decarboxylation and subsequent reduction of the acid in question with lithium aluminium hydride.

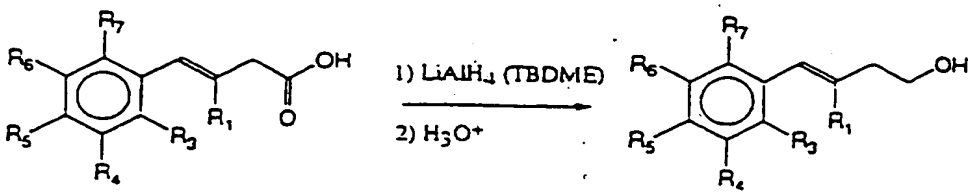


II

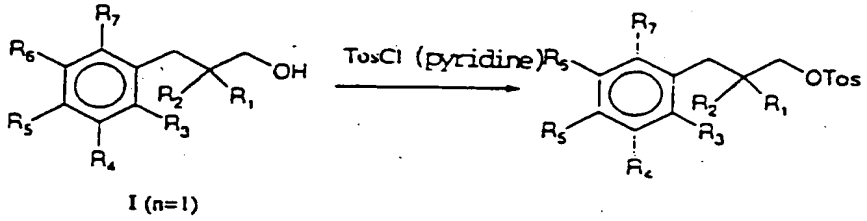
The alcohols of formula II with n = 2 are obtained for example from the respective alcohols with n = 1 via a chain elongation. The tosylate of alcohol II (n = 1) is substituted nucleophilically by NaCN and saponified. The resulting acid can be reduced with lithium aluminium hydride to the desired alcohol II (n=2).

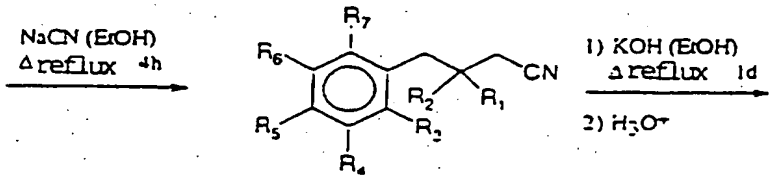


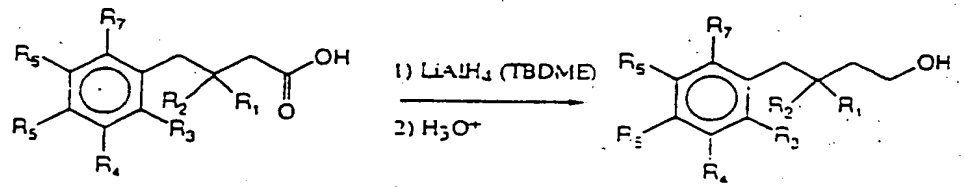
II (n=1)



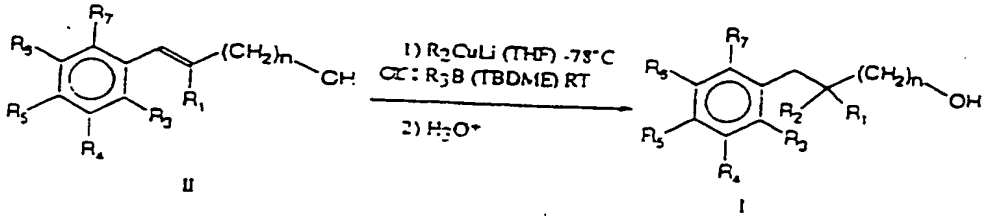
The alcohols I with n = 2 can be obtained in analogous manner.







By reducing alcohols of formula II with a reducing agent such as lithium aluminium hydride or alkylation agents such as lithium dialkyl cuprate or trialkyl boron, the alcohols of formula I can be obtained.



General synthesis instructions for alcohols of formula I using malonic acid diethyl ester

1. General instructions for the first alkylation of malonic acid diethyl esters:

200 mmol malonic acid diethyl ester and 200 mmol R_2-alkyl bromide (or chloride) are introduced first into a 250 ml triple-necked flask with internal thermometer, reflux condenser and dropping funnel and the whole is cooled to 10 to 15°C. 68.05 g (200 mmol) 20 % NaOEt in EtOH are slowly added dropwise (over 30 minutes) via a dropping funnel so that the temperature does not exceed 20°C. The mixture is then stirred for a further 30 minutes at 20°C and finally heated to 50 to 60°C for 1 hour. After cooling, the mixture is neutralized with glacial acetic acid (optionally cooling; pH monitored until the buffer pH value is reached). The resulting NaBr is separated off with a frit and then washed with a little cold EtOH. The main quantity of alcohol in the filtrate is distilled off at normal pressure. The filtrate is mixed with 50 ml H_2O and 1 ml conc. HCl, and the organic and the aqueous phases are separated from one another. The organic phase is kept for further use (see below) and the aqueous phase is extracted with 2 x 50 ml ether (if phase separation does not take place, the filtered-off NaBr is used to increase the density, as a result of which a phase separation is initiated). The combined organic phases are dried over sodium sulphate and the solvent is removed in a vacuum. The thus-formed crude product (R_2-substituted malonic ester) can be further used directly for the subsequent saponification.

2. General instructions for the second alkylation of alkyl malonic acid diethyl esters:

200 mmol R_2-substituted malonic acid diethyl ester and 200 mmol R_3-R_7-substituted benzyl bromide (or chloride) are introduced first into a 250 ml triple-necked flask with internal thermometer, reflux condenser and dropping funnel and the whole is

cooled to 10 to 15°C. 68.05 g (200 mmol) of 20 % NaOEt in EtOH are slowly added dropwise (over 30 minutes) via a dropping funnel so that the temperature does not exceed 20°C. The mixture is then stirred for a further 30 minutes at 20°C and finally heated to 50 to 60°C for 1 hour. After cooling, the mixture is neutralized with glacial acetic acid (optionally cooling; pH monitored until the buffer pH value is reached). The resulting NaBr is separated off with a frit and then washed with a little cold EtOH. The main quantity of alcohol in the filtrate is distilled off at normal pressure. The filtrate is mixed with 50 ml H_2O and 1 ml conc. HCl, and the organic and the aqueous phases are separated from one another. The organic phase is kept for further use (see below) and the aqueous phase is extracted with 2 x 50 ml ether (if phase separation does not take place, the filtered-off NaBr is used to increase the density, as a result of which a phase separation is initiated). The combined organic phases are dried over sodium sulphate and the solvent is removed in a vacuum. The thus-formed crude product (disubstituted malonic ester) can be further used directly for the subsequent saponification.

3. General instructions for the saponification of disubstituted malonic esters:

100 mmol of the disubstituted malonic ester are refluxed with a solution of 45 g conc. KOH (45%) and 50 ml EtOH for 3 hours. The main quantity of ethanol is distilled off under weak vacuum, the remaining residue is dissolved in H_2O until the water is clear and conc. HCl is added dropwise, accompanied by cooling with ice, until the pH value is 1. The aqueous phase is extracted with 100 ml and then 2 x 50 ml ether. The combined organic phases are dried over sodium sulphate, the solvent is removed in a vacuum and the remaining oil is dried over night in a desiccator. The crude product (disubstituted malonic acid) can be further used for the subsequent decarboxylation without further purification; small residual quantities of ethanol or water do not cause disturbance.

4. General instructions for the decarboxylation of disubstituted malonic acids:

The disubstituted malonic acid is heated for 3 hours at 180°C (CO_2 cleavage). Residual quantities of ethanol and H_2O and fruit esters are then distilled off at normal pressure (bath temperature 230 to 250°C). After applying a vacuum (20 to 25 mbar) the 2,3-disubstituted propionic acid is subjected to fractional distillation. To remove moisture that has distilled over and not very volatile components, the distillates can be dried in a desiccator.

5. General instructions for reducing disubstituted propionic acids with lithium aluminium hydride:

3.13 g (82.5 mmol) $LiAlH_4$ are introduced first into 100 ml of abs. ether. 100 mmol 2,3-disubstituted propionic acid in 50 ml ether are then slowly added dropwise (possibly with cooling), so that the ether boils easily. After the addition is finished, the mixture is stirred for a further 1 h at room temperature and then refluxed for 4 h. The cooled reaction mixture is carefully introduced with stirring into 200 ml iced water and stirred until the evolution of hydrogen is no longer to be observed. The whole is then mixed with 50 ml 10 % H_2SO_4, as a result of which the aluminium hydroxide precipitate dissolves. The phases are separated and the aqueous phase is extracted with 3 x 100 ml ether. The combined organic phases are washed with 3 x 50 ml of semi-concentrated NaOH and 2 x 50 ml saturated NaCl solution, dried over sodium sulphate and the solvent is removed in vacuum. The 2,3-disubstituted propanol is purified by distillation.

Synthesis examples

Selected as synthesis examples were

(±)-2-benzyl butanol (R_1=H; R_2=Et; R_3=R_4=R_5=R_6=R_7=H),

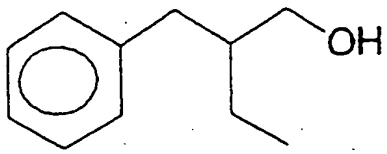
(±)-2-(3-methylbenzyl) butanol (R_1=H, R_2=Et; R_3=H; R_4=Et; R_5=R_6=R_7=H)

and

(±)-2-(3-chlorobenzyl) butanol (R_1=H, R_2=Et; R_3=H; R_4=Cl; R_5=R_6=R_7=H).

(±)-2-benzyl butanol:

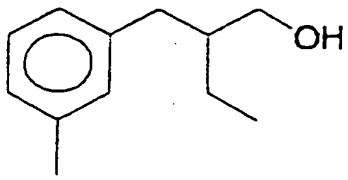
20 % total yield; colourless liquid with weak, pleasant odour; d = 0.975; n_D20 = 1.5178; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), approx. 1.65 (m; 1H, CH), 2.30 (s; 1H, OH), 2.60 (d; 2H, $ArCH_2$), 3.45 (d; 2H, CH_2OH), 7.0-7.4 ("s"; 5H, ArH).

(±)-2-(3-methylbenzyl) butanol:

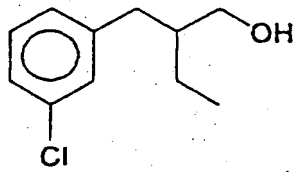
16 % total yield; colourless liquid with slight lily of the valley-type odour; d = 0.963; n_D20 = 1.5152; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), approx. 1.6 (m; 1H, CH), 2.25 (s; 3H, $ArCH_3$), 2.40 (s; 1H, OH), 2.55 (d; 2H, $ArCH_2$), 3.45 (d; 2H, CH_2OH), 6.7-7.2 (m; 4H, ArH).

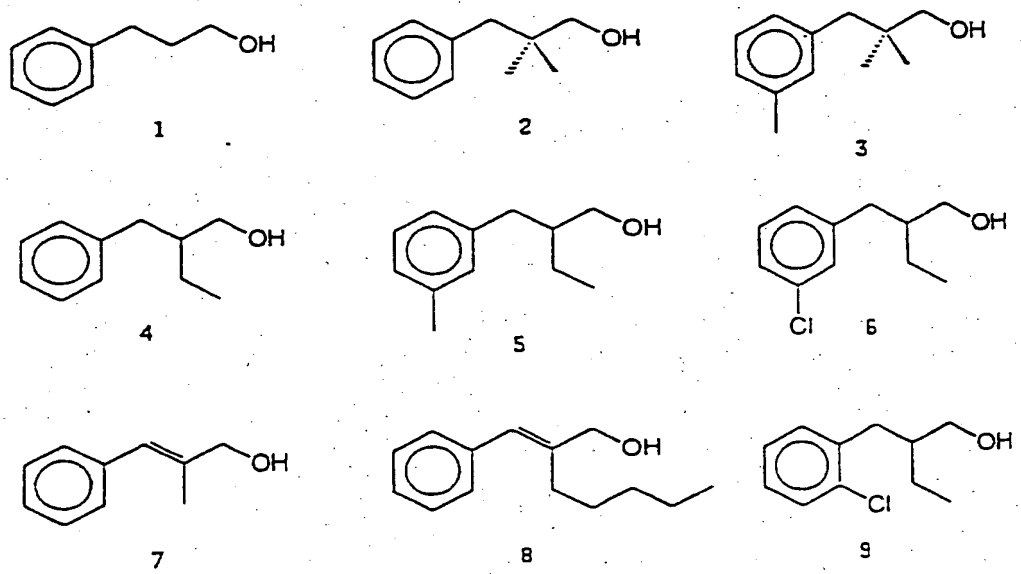
(±)-2-(3-chlorobenzyl) butanol:

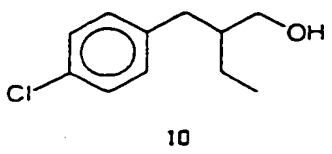
16 % total yield; slightly yellow liquid with discreet, pleasant odour; d = 1.099; n_D20 = 1.5322; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), 1.55 (m; 1H, CH), 2.55 (d; 2H, $ArCH_2$), 3.30 (s; 1H, OH), 3.45 (d; 2H, CH_2OH), 6.9-7.2 ("s"; 4H, ArH).

Formulae of the alcohols treated below:





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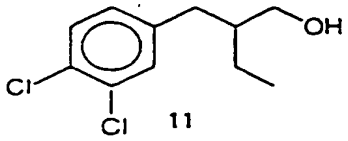

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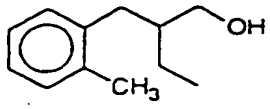

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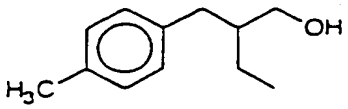

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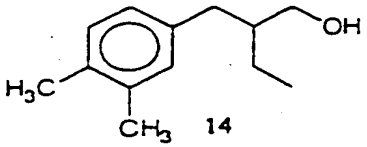

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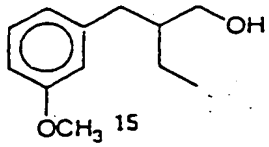

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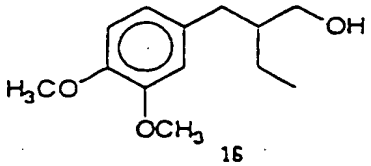

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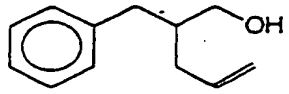

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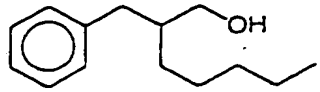


18

Applications

1. MIC (minimum inhibiting concentration) values

a) MIC values, water-soluble

Standard formulation:

–	Rewopal MPG 40	25.0 g
–	aromatic alcohol	10 mmol
–	dem.* water	to 100 g
–	lactic acid for adjusting the pH value to 7.0	q.s.

(*dem. = demineralized)

Test germs:	Staphylococcus aureus	ATCC 6538
	Proteus vulgaris	NCTC 4635
	Candida albicans	ATCC 10231
	Penicillium funiculosum	ATCC 36839
	Aspergillus niger	ATCC 6275

Test method:

In sterile test tubes, 5 ml each of the dilutions of the disinfectant in WSH (water of standardized hardness) are mixed with 5 ml double-concentrated casein peptone soybean flour peptone solution (CSL) or CSL and deactivating substances.

To determine the bacteriostatic action on Staphylococcus aureus and Proteus mirabilis the tubes are inoculated by adding 0.1 ml of a CSL culture diluted 1:10 with CSL and incubated for 24 h at 37°C.

To test the fungistatic action, 0.1 ml of an undiluted CSL culture of Candida albicans which has been incubated at 37°C for 72 h is used in each case. Evaluation takes place after 72 h at 37°C.

The highest dilution of the preparation in CSL or CSL and deactivating substances that still suppresses growth of the test germs after 12 h incubation serves as the measure of the multiplication-inhibiting action (inhibition titre).

In the case of the disinhibition tests, the culture media are to be adjusted to a pH value of 7.0 ± 0.2 according to the state of the disinfectant.

Data in µmol/100 ml test solution

	S. aureus	P. vulgaris	C. albicans	P. funi.	A. niger
Blank value	2,500	1,250	1,250	625	1,250
1	1,250	625	625	313	625
2	313	313	313	313	313
3	2,500	2,500	625	156	156
4	313	2,500	313	156	156
5	156	2,500	313	156	156
6	156	2,500	156	78	156
7	625	2,500	313	156	313
8	39	1,250	313	313	156

Standard formulation:

- aromatic alcohol 5.0 %
- Brij 58 5.0 %
- 1,3-butanediol to 100

Test germs: see above
Test method: see above

Data in µmol/100 ml test solution

Compd. No.	S. aureus	P. vulgaris	C. albicans	P. funi.	A. niger
Blank value	2,500	1,250	1,250	625	1,250
1	1,250	625	625	313	625
3	625	625	625	313	625

Compared with the parent compound 3-phenyl propanol (alcohol Compd. No. 1), the alcohols 2-8 according to the invention clearly display

microbistatic activities, particularly alcohols 2, 6 and 8, in almost ten times lower a use concentration.

b) MIC values, water-insoluble

Solutions of the aromatic alcohols in acetone (w/w)

Test germs:	Staphylococcus aureus	ATCC 6538
	Escherichia coli	ATCC 11229
	Candida albicans	ATCC 10231
	Aspergillus niger	ATCC 6275

Test method: as under 1.; the dilution solutions were prepared in acetone.

The size of the covered areas of the plates is given in %; 100% means no inhibiting action.

Alcohol	Concentration [% by wt.]	S. aureus	E. coli	C. albicans	A. niger
Blank value	0.00	100%	100%	100%	100%
9	1.00	80%	100%	80%	20%
	0.50	100%	100%	100%	90%
	0.25	100%	100%	100%	100%
10	1.00	10%	100%	10%	10%
	0.50	100%	100%	90%	70%
	0.25	100%	100%	100%	90%
	0.125	100%	100%	100%	100%
11	1.00	5%	90%	10%	10%
	0.50	90%	100%	80%	70%
	0.25	100%	100%	100%	100%
12	1.00	90%	100%	80%	80%
	0.50	100%	100%	100%	100%
13	1.00	90%	95%	90%	20%
	0.50	100%	100%	100%	90%
	0.25	100%	100%	100%	100%
14	1.00	30%	100%	20%	10%
	0.50	90%	100%	100%	80%
	0.25	100%	100%	100%	90%
	0.125	100%	100%	100%	100%
15	1.00	100%	100%	100%	90%
	0.50	100%	100%	100%	100%
17	1.00	100%	90%	100%	80%
	0.50	100%	100%	100%	100%
18	1.00	0%	100%	70%	0%
	0.50	20%	100%	80%	40%
	0.25	100%	100%	100%	100%

Alcohols 11 and 13 display a very good broad activity spectrum. In contrast, alcohols 10, 14 and 18 display a very good selective action, in particular against fungi and yeasts.

2. Antimicrobial effectiveness in the plate diffusion test

Standard formulation:

- aromatic alcohol 1 part
- dimethylformamide 6 parts

Test germs:	Staphylococcus aureus	ATCC 6538
	Pseudomonas aeruginosa	ATCC 15442
	Proteus mirabilis	ATCC 14153
	Escherichia coli	ATCC 11229
	Candida albicans	ATCC 10231

Test method: Agar diffusion test

The diameters of the inhibition zones are given in mm.

Alcohol	S. aureus	P. aeruginosa	P. vulgaris	E. coli	C. albicans
Blank value	0	0	0	0	0
9	15	0	0	11	15
10	14	0	0	11	15
11	17	0	0	0	13
12	20	15	13	17	22
13	16	13	14	13	19
14	18	18	0	15	22
15	18	15	18	18	23
16	18	18	17	17	28
17	16	12	13	13	17
18	11	0	0	0	11

Alcohols 12, 15 and 16 show a very strong inhibition of the tested germs, alcohols 13, 14 and 17 showing a strong inhibition.

3. Use in an alcoholic surface disinfectant

Standard formulation:

- ethanol (MEK denatured) 25.0 %
- 1-propanol 35.0 %
- perfume 0.02 %
- benzotriazole 0.001 %
- Marlipal 013/70 0.1%
  (isotridecanpolyethyleneglycol-(7)-ether = C_{13} oxo alcohol + 7 mol ethylene oxide)
- active ingredient additive x%
- dem. water to 100

Test germ: Ps. aeruginosa
Test method:

Quantitative surface test according to DGHM (Deutsche Gesellschaft für Hygiene and Microbiology = German Association for Hygiene and Microbiology). In order to exclude the effectiveness of the readily volatile alcohol components (ethanol, 1-propanol), the preparations were deposited onto the surfaces and the germs were deposited after approx. 20 minutes.

Test surfaces: PVC and OP tiles
Data as reduction factors (log stages)

Additive	PVC			Tiles		
	30'	60'	240'	30'	60'	240'
without additive	0	0	0	0	0	0
0.05 % phenoxyethanol	0	0	0	0	0	0
0.05% phenoxyethanol 0.01% imidazole	0	0	0	0	0	0
0.125% Vantocil IB (polyhexamethylene biguanid hydrochlorid) 0.025% sorbic acid	0	0	0	0	0	0
0.027% Hostapur SAS (sec.alkanesulphonate-Na-salts based on n-paraffins) 0.006% Na-laurylether sulphate 0.017% malic acid	0	0	0	0	0	0
0.05% 3-phenyl propanol (1)	0	0	0	0	0	0
0.05% 2,2-dimethyl-3-phenyl-1-propanol (2)	>6.0	>5.4	>6.5	4.1	4.9	>5.8

Only the preparation with an aromatic alcohol of the formula I according to the invention, 2,2-dimethyl-3-phenyl-1-propanol (2) has an effectiveness against Pseudomonas aeruginosa on PVC and tiles that increases with increasing action time.

The other preparations are disinfectant solutions.

4. Use in a foot spray with deodorizing action and simultaneous prevention of athlete's foot

Formula:

- 2-propanol 40.0%
- aromatic alcohol 0.2 %
- allantoin 0.5 %
- dem. water to 100

Test germs: special skin fungi such as Trichophyton rubrum, Trichophyton mentagrophytes (ATCC 9533), Microsporon gypseum

Test method: Determination of the minimum inhibition concentration (method see under 1.) Data in %

Alcohol	T. rubrum	T. mentagrophytes	M. gypseum
Blank value	12.5%	6.25%	6.25%
1	6.25%	6.25%	6.25%
6	1.56%	1.56%	3.13%
8	1.56%	1.56%	1.56%

Test germs: special skin fungi such as Trichophyton rubrum, Trichophyton mentagrophytes, Microsporon gypseum

Test method: Agar diffusion test
Data as millimetres inhibition zone

Alcohol	Use concentration	T. rubrum	T. mentagrophytes	M. gypseum
Blank value	100%	0 mm	0 mm	0 mm
1	100%	0 mm	0 mm	0 mm
6	100%	12 mm	15 mm	13 mm
8	100%	23 mm	22 mm	19 mm
	50%	14 mm	14 mm	10 mm

With typical fungi which are relevant as regards skin, the formulations with alcohols 6 and 8 according to the invention show a very good action both in the MIC test and in the agar diffusion test. The aforementioned formulations are thus suitable for use in deodorants and products for the prevention of athlete's foot.

The parent compound 3-phenyl propanol shows almost similar values as the blank value, i.e. is ineffective.

5. Preservative

Standard formulation:

- sulfosuccinate 12.0%
- betaine 3.0%
- aromatic alcohol 0.5%
- re-fatting agent
- skin care additives
- thickener
- dem. water to 100

Test germs: Germ mixture of Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, Klebsiella pneumoniae, Enterobacter gergoviae, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas putida, Aspergillus niger,

Penicillium funiculosum, Candida albicans; Total germ count 10^8-10^9/ml.

Test method: weekly loading of the sample with germ suspension; smear onto CS and Sabouraud agar. See also K.-H. Diehl, P. Oltmanns, J. Ramsbotham, Seife, Öle, Fette, Wachse 118 (1992) 546.

Data expressed semi-qualitatively:

-	no growth	< 10^2 CFU/g	(CFU = colony-forming units)
+	slight growth	approx. 10^3 CFU/g	
++	moderate growth	approx. 10^4-10^5 CFU/g	
+++	heavy growth	> 10^5 CFU/g	

Alcohol	1st week	2nd week	3rd week	4th week	5th week
Blank value	+++	+++	+++	+++	+++
Phenoxyethanol	-	-	-	-	-
1	+	+	-	-	-
2	-	-	-	-	-

Preservation with 0.5 % 2,2-dimethyl-3-phenyl propanol (2) is just as effective as that with the known preservative phenoxyethanol, but displays a more sure (more quickly acting) preservation in the first two weeks compared with the parent compound 3-phenyl propanol.

The alcohols according to the invention are thus suitable as a preserving additive in shampoos and shower gels.

6. Mucous membrane antiseptic

Standard formulation:

-	Cocamidopropyl betaine (30%)	3.0 %
-	glycerin DAB 10 (85%)	0.5%
-	phenoxyethanol	1.0%
-	arom. alcohol	0.5%
-	dem. water	to 100
-	NaOH to adjust the pH value to 5.5	q.s.

Test germs: Pseudomonas aeruginosa ATCC 15442
Staphylococcus aureus ATCC 6538

Test method: Quantitative suspension test according to DGHM

Data as reduction factors (log stages); C = control

pH 5.5	Alcohols:	none (blank value)			1			2			3			8		
Test organisms	Contact time [min]	C	100	50	C	100	50	C	100	50	C	100	50	C	100	50
Staphylococcus aureus	30''	6.7	0	0	6.6	2.7	1.1	6.6	1.3	0	6.6	2.0	1.0	6.7	2.7	0
	1'	6.7	0	0	6.6	3.2	1.2	6.8	4.6	1.8	6.6	3.4	1.4	6.7	3.9	0
	2'	6.7	1.3	0	6.8	4.1	1.6	6.6	5.6	2.8	6.7	3.8	2.0	6.7	5.1	0
	5'	6.8	2.1	0	6.7	5.2	1.9	6.8	>5.8	4.4	6.7	4.9	3.3	6.8	>5.8	2.6
Pseudomonas aeruginosa	30''	6.5	3.3	0	6.5	>5.5	0	6.4	3.7	0	6.4	2.3	0	6.5	4.0	0
	1'	6.5	4.1	0	6.5	>5.5	0	6.5	5.2	0	6.5	2.7	0	6.5	4.4	0
	2'	6.6	4.5	0	6.5	>5.5	1.1	6.4	>5.4	0	6.4	2.9	0	6.6	5.0	0
	5'	6.6	5.6	0	6.6	>5.6	1.3	6.6	3.6	0	6.6	3.7	0	6.6	5.6	0
Candida albicans	30''	5.9	0	0	6.1	1.0	0.7	5.9	1.6	0.6	5.9	2.9	0.7	5.9	1.9	0
	1'	6.1	0	0	6.4	1.8	1.1	5.5	2.3	0.1	5.5	4.0	0.3	6.1	2.9	0
	2'	6.0	0	0	5.8	2.7	0.4	5.4	2.4	0.1	5.4	>4.4	0.4	6.0	3.4	1.1
	5'	6.0	0	0	5.9	4.9	0.4	5.3	4.3	0.2	5.3	>4.3	0.9	6.0	5.0	2.0

The alcohols according to the invention significantly increase the effectiveness against the aforementioned germs, in particular against yeasts.

7. Skin antiseptic

a) standard formulation:

- 1-propanol	30.0%
- 2-propanol	45.0%
- aromatic alcohol	1.0%
- dem. water	to 100

Test germ: Microsporon luteus ATCC 15442

Test method: Apply 0.2 ml preparation to 10cm^2 skin, allow to dry, cover with TEGADERM® film and leave to work for 1 h, contaminate with 0.1 ml germ suspension, remove after 15 minutes with ring method

Reference: Control against Neo-Kodan®

Number of subjects: 10 subjects

Data as average value of the reduction factors (RF in log stages) of all 10 subjects

aromatic alcohol	Average value of RF
1.0% phenyl propanol (1)	0
1.0% α-amyl cinnamyl alcohol (8)	1.9
Reference: Neo-Kadan®	1.9

The formulation with 1.0% α-amyl cinnamyl alcohol (8) also shows the same values in the suspension test according to DGHM as the skin antiseptic Neo-Kadan® used for reference of 50%, 30 seconds, and likewise shows an equal action against the resident skin flora (100%, 15 seconds).

Moreover, the aforementioned results show that an action against the transient flora is only guaranteed when the α-amyl cinnamyl alcohol (8) substituted according to formula II is used and not the parent compound 3-phenyl propanol (1).

b) Standard formulation:

-	1-propanol	15.0%
-	2-propanol	30.0%
-	aromatic alcohol	1.0%
-	dem. water	to 100

Test germs:	Staphylococcus aureus	ATCC 6538
	Pseudomonas aeruginosa	ATCC 15442
	Candida albicans	ATCC 10231

Test method: Quantitative suspension test according to DGHM

Data as reduction factors (log stages)

		Blank value (0% 8)				1.0% 8		
Test organisms	Contact time [min]	C	75	50	25	75	50	25
Staphylococcus aureus	30''	6.6	>5.6	>5.6	0	>5.6	>5.6	2.8
	1'	6.5	>5.5	>5.5	0	>5.5	>5.5	3.6
	2'	6.9	>5.9	>5.9	0	>5.9	>5.9	4.7
	5'	6.8	>5.8	>5.8	0	>5.8	>5.8	>5.8
Pseudomonas aeruginosa	30''	6.6	>5.6	>5.6	0	>5.6	>5.6	0
	1'	6.8	>5.8	>5.8	0	>5.8	>5.8	0
	2'	6.7	>5.7	>5.7	0	>5.7	>5.7	0
	5'	6.7	>5.7	>5.7	0	>5.7	>5.7	0
Candida albicans	30''	5.6	>4.6	0.9	0.2	>4.6	2.7	0.5
	1'	5.6	>4.6	1.5	0	>4.6	3.5	0.6
	2'	5.9	>4.9	2.4	0.4	>4.9	>4.9	1.1
	5'	6.1	>5.1	3.5	0	>5.1	>5.1	1.7

In the aforementioned propanol-reduced formulation, the additional action of the α-amyl cinnamyl alcohol is seen in particular in the case of Candida albicans.

8. Use in an alcoholic disinfectant for surgical hand disinfection

Formulation:

- ethanol 80.0%
- phenethyl alcohol 2.0%
- 2,2-dimethyl-3-(3-methylphenyl) propanol (3) 0.4%
- re-fatting agent
- humectant
- dem. water to 100

The requirements of the DGHM guideline for surgical hand disinfection are satisfied by the aforementioned formula both in their immediate action and also in their long-term action.

A formulation which contains neither phenethyl alcohol nor 2,2-dimethyl-3-(3-methylphenyl) propanol (3) does not satisfy these requirements.

9. Effectiveness against M. terrae S in the germ carrier experiment with standard cotton

Standard formulation:

-	Rewopal MPG 40	25.0%
-	aromatic alcohol	2.0 %
-	dem. water	to 100

Test germ: Mycobacterium terrae ATCC 15755

Test method: Production of the germ carriers: To prepare the germ carriers, standard cotton fabric is used which has been thoroughly rinsed in double-distilled water. The fabric is cut into pieces measuring approximately 1 cm^2, sterilized in a autoclave and dried.

Production of the bacterial suspension:

The bacteria are elutriated with 5 ml CSL from a 24 h-old (37°C) culture onto CSA plates measuring approx. 9 cm in diameter, the suspension being diluted with CSL if necessary. The number of CFU/ml is to be determined using surface culture. It should be > 10^9/ml.

Procedure for the germ carrier test:

The sterilized and dried germ carriers are introduced into the bacterial suspension and left in it for 15 minutes, during which they are turned over twice.

A number (4) of contaminated, thoroughly impregnated germ carriers, corresponding to the proposed removal times - 15, 30, 60 and 120 minutes - is placed in a small dish and 10 ml of the disinfectant solution to be tested in WSH are poured over them. Air bubbles are to be removed by repeated turning of the germ carriers.

After the corresponding action times, the germ carriers are to be removed from the disinfectant solution, and after rinsing twice in each case for 1 min in 10 ml ML solution (see Appendix) to which the deactivating substances were optionally added, the germ carriers are placed onto the surface of a Löwenstein-Jensen nutrient medium with tweezers and moved backwards and forwards 3 to 4 times using light pressure. After inoculating the nutrient medium surface the small cloth is to remain lying directly above the condensed water level of the nutrient medium.

Germ carriers pre-treated in the same way, but kept in WSH for 120 minutes instead of in disinfectant solution are to be inoculated as a control. The inoculated tubes are incubated at 37°C for 3 weeks.

Data expressed qualitatively:

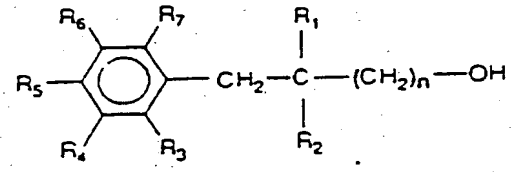
E	individual colonies	++	moderate growth
M	several colonies	+++	heavy growth
+	weak growth	++++	very heavy growth
∞	lawn growth		

Alcohol	15'	30'	60'	120'
none	∞	∞	∞	∞
1	+ + + +	+ + + +	+ + +	+ + +
2	+ + +	+ +	+	M
3	+ + +	+	+	E
7	+ + +	+ +	+ +	+
8	+ + +	+ +	+	E

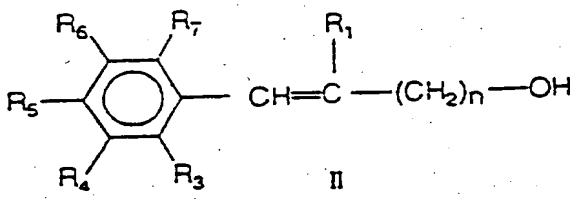
The alcohols according to the invention, particularly 2, 3 and 8, show a very good action against mycobacteria with relatively long action times and are therefore suitable for use in instrument disinfectants. The parent compound 1 shows a very much weaker action.

Patent claims

1. A compound of formula I or II,



I



II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

with the proviso, that in compounds of formula I

i) where R_1 and all groups R_3 to R_7 are hydrogen, then n = 2;

ii) where R_1 and R_2 are C_1-C_6 alkyl and all groups R_3 to R_7 are hydrogen, then n =2;

iii) where R_1, R_2 and R_4 are methyl and all groups R_3 and R_5 to R_7 are hydrogen, then n =2;

iv) where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is methyl or methoxy, then n = 2;

v) where R_1, R_3, R_6 and R_7 are hydrogen, R_2 is methyl and R_4 and/or R_5 are H or C_1-C_6 alkyl, then n = 2;

vi) where R_1 and R_4 to R_7 are hydrogen, R_2 is methyl and R_3 is methyl or methoxy, then n = 2;

vii) where R_1, R_3, R_5 and R_7 are hydrogen, R_2 is methyl, R_4 and R_6 are methyl or R_4 is hydrogen and R_6 is methyl, then n = 2;

and with the proviso, that in compounds of formula II

where R_1 is methyl or pentyl and all other groups R_3 to R_7 are hydrogen, then n = 2.

2. A compound according to claim 1, in which

in which

R_2 is selected from C_1-C_5 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_5 alkenyl and C_3-C_5 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is hydrogen, fluorine, chlorine or bromine.

3. A compound according to claim 1 or 2 in which
R_2 is methyl ethyl, ethenyl, propyl, propenyl, propargyl,

butyl and amyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, is hydrogen, methyl-X-, ethyl-X-, ethenyl-X-, propyl-X-, propenyl-X-, propargyl-X, isopropyl-X, isopropenyl-X-, t-butyl-X-, methoxymethyl-X-, methoxyethyl-X-, ethoxymethyl-X-, ethoxyethyl-X-, methoxypropyl-X- or ethoxypropyl-X-, where X is -O- or -S-.

4. A compound according to any of the preceding claims in which n = 1.

5. A compound according to one of claims 1 to 4 which is (±)-2-benzyl butanol, (±)-2-(3-methylbenzyl) butanol or (±)-2-(3-chlorobenzyl) butanol.

6. Composition which contains at least one compound of formula I or II according to one of claims 1 to 5 and a compound selected from alcohols, surfactants and solvents.

7. Composition according to Claim 6 which contains a compound of formula I or II in a quantity of 0.01 to 10 % by wt., in particular 0.05 to 8 % by wt. and preferably 0.1 to 5 % by wt.

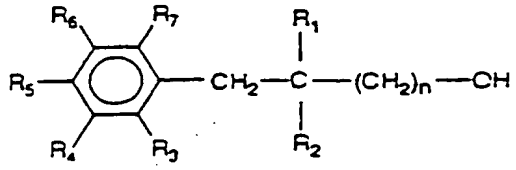
8. Composition according to claim 6 or 7 which contains

a) 0.01 to 10 % by wt. of a compound of formula I or II, and

b) 0.1 to 90 % by wt. of a compound selected from C_1-C_6 alkyl alcohols, unsubstituded or substituted with a C_6-C_{12} aryl, aralkyl or aryloxy group, anionic, cationic, amphoteric or nonionic surfactants, dimethylformamide, betaines and glycerine.

9. Composition according to any of claims 6 to 8 which is a disinfectant, antiseptic, antimycotic, deodorant or preservative.

10. Process for the production of a compound of formula I



I

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

wherein

a) a malonic acid dialkyl ester is monoalkylated, as a result of which the group R_2 is introduced,

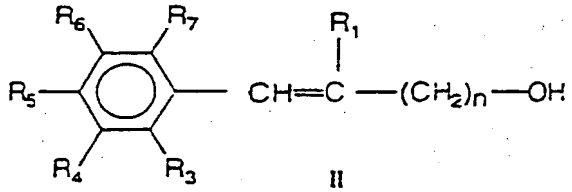
b) the monoalkylated malonic acid alkyl ester is dialkylated with a benzyl halide optionally substituted at the aromatic ring, as a result of which the groups R_3 to R_7 are introduced, provided they are not hydrogen,

c) the dialkylated malonic acid dialkyl ester is saponified and decarboxylated, as a result of which the corresponding-

ly 3-aryl-substituted propionic acid results and

d) this 3-aryl-substituted propionic acid is reduced with the formation of the desired alcohol of formula I.

11. Process for the production of a compound of formula II



II

in which

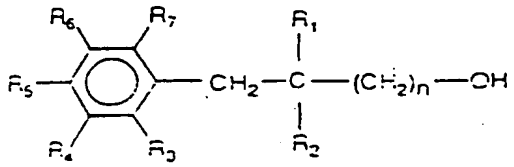
R_1 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

each of R_3 to R_7, independently, is a significance of R_1, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

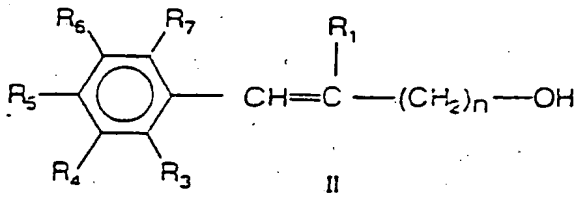
n is 1 or 2,

wherein in the case of n = 1 a corresponding aromatic aldehyde is condensed with an anhydride with simultaneous decarboxylation and then the resulting acid is reduced with lithium aluminium hydride, or in the case of n = 2 the tosylate of the respective alcohol with n = 1 is substituted nucleophilically by NaCN and is saponified and the resulting acid is reduced with lithium aluminium hydride to give the desired alcohol.

12. Use of a compound of formula I or II



I



II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

as biocidal active ingredients.

INTERNATIONAL SEARCH REPORT

Inv onal Application No
PCT/EP 95/05068

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C33/20 C07C33/46 C07C33/30 A61K31/045

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON, vol. 50, no. 25, 20 June 1994, OXFORD, GB, pages 7343-7366, XP002000718 D.P. CURRAN, ET AL.: "Amide-based protecting/radical translocating (PRT) groups. Generation of radicals adjacent to carbonyls by 1,5-hydrogen transfer reactions of o-iodoanilides" see compound 62 --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1996	03.05.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 168, no. 1, 13 March 1979, LAUSANNE, CH, pages 1-11, XP002000719 J.G. DUBOUDIN, ET AL.: "Réactifs de Grignard vinyliques gamma fonctionnels. I. Réactivité des organomagnésiens vis-à-vis d'alcools alpha acétyléniques en présence d'halogénures cuivreux" see table 4 ---	1-4
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 53, no. 7, July 1931, WASHINGTON, DC, US, pages 2747-2755, XP002000720 M.T. BOGERT, ET AL.: "Researches on aldehydes. IV. The catalytic reduction of simple and of substituted cinnamic aldehydes" see page 2752 - page 2755 ---	1-4
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 53, no. 4, April 1931, WASHINGTON, DC, US, pages 1605-1609, XP002000721 M.T. BOGERT, ET AL.: "The synthesis of simple and of substituted 2-alkylcinnamic alcohols, including a monomolecular cubebin" see page 1607 - page 1609 ---	1-4
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 88, no. 24, 20 December 1966, WASHINGTON, DC, US, pages 5809-5816, XP002000722 J.R. OWEN, ET AL.: "The migration aptitude of substituted benzyl vs. methyl in carbonium ion reactions of the 2,2-dimethyl-3-aryl-1-propyl system. The question of alkyl participation" see page 5813 ---	1-4
X	BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 67, 1934, WEINHEIM, DE, pages 1696-1712, XP002000742 J. VON BRAUN, ET AL.: "Die Unstzung von Aldehyden mit Metallen und ihre katalytische Druck-Hydrierung" see page 1707 ---	5
X	US,A,4 115 578 (G.A. MILLER, ET AL.) 19 September 1978 see column 5; example 67 ---	10

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/05068

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 110 430 (R. HOPP, ET AL.) 29 August 1978	12
A	see the whole document	1-9

X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, DEUXIEME PARTIE - CHIMIE ORGANIQUE, BIOCHIMIE., no. 7-8, July 1974 - August 1974, PARIS, FR, pages 1607-1613, XP002000723 A. CARD, ET AL.: "Recherches dans la série des métallocènes. XXIX. Synthèse de benchrotrénocyclohexénones substituées par un reste isopropyle" see page 1610, right-hand column - page 1611, left-hand column; table I	10

A	US,A,4 691 043 (H. DEMARNE, ET AL.) 1 September 1987 see the whole document	1,9

A	US,A,4 720 581 (M. MOSSE, ET AL.) 19 January 1988 see the whole document	1,9

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/05068

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched incompletely: 1-4, 6-12
Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Inconsistencies

The compound (+/-)-2-benzylbutanol claimed specifically by name in Claim 5 is excluded (by the first "proviso") from the scope of Claim 1 upon which Claim 5 is dependent. This compound was however included in the scope of the search for Claims 5-9, and it was revealed to have been reported in the literature on many occasions [the first as early as 1908 (see *Comptes rendus*, 1908, **146**, 1406)].

General comment

A structure search in the databases of the Chemical Abstracts Service and of Beilstein revealed many compounds falling within the scope of Claim 1, and no attempt was made to include more than a representative sample in the search report for Claims 1-4 and 6-8, concentrating on compounds prepared according to the methods of Claims 10 and 11 and those being used for the applications listed in Claims 9 and 12.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/05068

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		AU-B-	502679	02-08-79
		AU-B-	1087376	11-08-77
		CA-A-	1065323	30-10-79
		CH-A-	619697	15-10-80
		DE-A-	2604047	16-09-76
		FR-A,B	2300081	03-09-76
		GB-A-	1530172	25-10-78
		JP-A-	51143667	10-12-76
		NL-A-	7601206	09-08-76
		OA-A-	5234	28-02-81
		SE-A-	7600674	06-08-76
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		CH-A-	609861	30-03-79
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		JP-B-	61006042	24-02-86
		NL-A-	7501130	05-08-75
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		CA-A-	1271416	10-07-90
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		EP-A,B	0135433	27-03-85
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		JP-A-	60120801	28-06-85
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/05068

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4720581		AU-B- 563648	16-07-87
		AU-B- 3079084	07-02-85
		CA-A- 1238922	05-07-88
		EP-A,B 0136195	03-04-85
		JP-A- 60054351	28-03-85
		SU-A- 1319784	23-06-87